Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy

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Abstract: BACKGROUND: Takotsubo cardiomyopathy (TC) usually is not recognized until heart catheterization reveals typical wall motion abnormalities in the absence of significant coronary artery disease. It was our aim to identify TC by its unique cardiac biomarker profile at an early stage and, preferably, with non-invasive procedures only. METHODS: Ratios of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and myoglobin, NT-proBNP and troponin T (TnT), NT-proBNP and creatinekinase-MB (CK-MB) were compared in patients with TC (n=39), patients with ST-elevation myocardial infarction (STEMI, n=48) and patients with non-ST-elevation myocardial infarction (NSTEMI, n=34). Biomarkers were recorded serially at admission and at the three consecutive days. Optimal cut-off values to distinguish TC from STEMI and NSTEMI were calculated with receiver operator characteristic (ROC) curves. RESULTS: At admission a NT-proBNP (ng/l)/myoglobin (g/l) ratio of 3.8, distinguished TC from STEMI (sensitivity: 89%, specificity: 90%), while a NT-proBNP (ng/l)/myoglobin (g/l) ratio of 14 separated well between TC and NSTEMI (sensitivity: 65%, specificity: 90%). Best differentiation of TC and ACS was possible with the ratio of peak levels of NT-proBNP (ng/l)/TnT (g/l). A cut-off value of NT-proBNP (ng/l)/TnT (g/l) ratio of 2889, distinguished TC from STEMI (sensitivity: 91%, specificity: 95%), while a NT-proBNP (ng/l)/TnT (g/l) ratio of 5000 separated well between TC and NSTEMI (sensitivity: 83%, specificity: 95%). CONCLUSIONS: TC goes along with a singular cardiac biomarker profile, which might be useful to identify patients with TC among patients presenting with acute coronary syndromes (ACS).

DOI: https://doi.org/10.1016/j.ijcard.2011.09.077

IJC-D-11-01099 R1

July 19th, 2011

Takotsubo Cardiomyopathy has a Unique Cardiac Biomarker Profile: *NT-proBNP / Myoglobin and NT-proBNP / Troponin T Ratios for the Differential Diagnosis of Acute Coronary Syndromes and Stress Induced Cardiomyopathy*

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Short title: Fröhlich et al. An alternative diagnostic approach to Takotsubo

Conflicts of interest disclosure: The authors declare no conflicts of interest.

Word count: 3593

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ABSTRACT

Background: Takotsubo cardiomyopathy (TC) usually is not recognized until heart catheterization reveals typical wall motion abnormalities in the absence of significant coronary artery disease. It was our aim to identify TC by its unique cardiac biomarker profile at an early stage and, preferably, with non-invasive procedures only.

Methods: Ratios of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and myoglobin, NT-proBNP and Troponin T (TnT), NT-proBNP and creatinekinase-MB (CK-MB) were compared in patients with TC (n=39), patients with ST-elevation myocardial infarction (STEMI, n=48) and patients with non-ST-elevation myocardial infarction (NSTEMI, n=34). Biomarkers were recorded serially at admission and at the three consecutive days. Optimal cut-off values to distinguish TC from STEMI and NSTEMI were calculated with Receiver Operator Characteristic (ROC) - curves.

Results: At admission a NT-proBNP (ng/l) / myoglobin (µg/l) ratio of 3.8, distinguished TC from STEMI (sensitivity: 89%, specificity: 90%), while a NT-proBNP (ng/l) / myoglobin (µg/l) ratio of 14 separated well between TC and NSTEMI (sensitivity: 65%, specificity: 90%). Best differentiation of TC and ACS was possible with the ratio of peak levels of NT-proBNP (ng/l) / TnT (µg/l). A cut-off value of NT-proBNP (ng/l) / TnT (µg/l) ratio of 2889, distinguished TC from STEMI (sensitivity: 91%, specificity: 95%), while a NT-proBNP (ng/l) / TnT (µg/l) ratio of 5000 separated well between TC and NSTEMI (sensitivity: 83%, specificity: 95%).

Conclusions: TC goes along with a singular cardiac biomarker profile, which might be useful to identify patients with TC among patients presenting with acute coronary syndromes (ACS).

Keywords**:** Acute coronary syndrome, takotsubo cardiomyopathy, NT-proBNP

Abbreviations list:

AUC	Area under the curve
CAD	Coronary artery disease
IR	Interquartile range
NSTEMI	Non-ST elevation myocardial infarction
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
ROC	Receiver operator characteristic (curve)
STEMI	ST-elevation myocardial infarction
TC	Takotsubo cardiomyopathy

INTRODUCTION

Takotsubo cardiomyopathy (TC), also known as stress induced cardiomyopathy or apical ballooning syndrome, was first described by Dote in 1991.[1] It is defined as a fully reversible acute deterioration of left-ventricular function, which is mainly found in women after an episode of emotional or physical stress (e.g. psychosocial stress, sepsis, surgery).[2] TC is an important differential diagnosis of ST-elevation (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI) and has an estimated incidence of 1 to 2 per cent or 7000 to 14000 patients admitted to emergency departments in the U.S. for acute coronary syndromes.[2] As patients with TC – in contrast to those with STEMI or NSTEMI – have a favorable prognosis; diagnosis should be made early and preferably non-invasively.[2] However, in the majority of patients TC is not recognized until cardiac catheterization reveals typical wall motion abnormalities in the absence of significant coronary artery disease. Consequently, diagnostic algorithms are needed to safely separate patients with acute myocardial ischemia, who qualify for an invasive treatment strategy, from those who do not, such as patients with TC. However, neither symptoms on admission, nor ECG changes are useful in the differentiation of TC from acute myocardial infarction.[3-5] Of note, troponin, creatinekinase (CK), CK-MB and myoglobin levels are only slightly elevated in the majority of patients with TC.[6] In contrast, a pronounced increase in brain natriuretic peptide (BNP) is often seen in stress-induced cardiomyopathy.[7]

We thought to elucidate whether TC can be identified among patients admitted for suspected acute coronary syndromes by its distinct cardiac biomarker profile only.

METHODS

Patient population

Patients with TC were compared to patients with STEMI or NSTEMI. STEMI and NSTEMI were defined according to the guidelines of the European Society of Cardiology.[8, 9] Patient data were retrospectively retrieved from our database (years 2004 – 2009) and patients in the STEMI and NSTEMI group were matched for age and gender to those of the TC group. All patients underwent coronary angiography. Patients with known ischemic, dilative or valvular cardiomyopathy or severe renal insufficiency (defined as glomerular filtration rate < 30 ml/min at admission, calculated with the MDRD formula [10]) or paced cardiac rhythm were excluded. Glomerular filtration rate (GFR) was documented as "> 60 ml/min" or lower, as the MDRD formula can only be applied appropriately in the setting of a GFR lower than 60 ml/min.

Patients in the TC group had to meet the proposed Mayo Clinic criteria[2] for Takotsubo cardiomyopathy:

- Transient hypokinesis, akinesis or dyskinesis of the left ventricular mid segments with or without apical involvement. The regional wall motion abnormalities typically extend beyond a single epicardial coronary distribution. A stressful trigger is often, but not always present.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- New electrocardiographic abnormalities (either ST-segment elevation and/or T wave inversion) or modest elevation in cardiac troponin.
- Absence of pheochromocytoma or myocarditis.

Electrocardiographic analysis

ECGs obtained on arrival at the emergency department were analyzed by two physicians according to ESC guidelines.[11]

Laboratory measurements

Blood samples were taken every 8 hours during the first 24 hours after hospital admission, every 12 hours the following day and every 24 hours thereafter for, at least, 2 days. Time from onset of chest pain to drawing of the first blood sample was measured, as well as the period from onset of pain to the peak NT-proBNP and TNT levels. Further, some commonly used markers of myocardial necrosis — CK and CK-MB — were measured. Myoglobin, representing one of the earliest markers of myocardial necrosis was measured at entry only. Peak CRP levels were recorded. Blood samples were analyzed using the cobas® analyzer (Roche Diagnostics, Basel, Switzerland) at the Institute of Clinical Chemistry of the University Hospital Zurich.

Follow-up of Takotsubo patients

Baseline and follow-up ejection fraction was assessed using echocardiography according to standard procedures.[12] Clinical follow-up was retrospectively obtained from our clinical database according to follow-up visits.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (SPSS Schweiz AG, Zurich, Switzerland). Continuous variables are presented as median with the interquartile range (25. – 75. percentile) in brackets. For evaluation of normal distribution the Kolmogorov-Smirnoff test was used. To identify significant differences between the TC, the STEMI and the NSTEMI groups, the Chi-square test was used

for categorical variables and the Kruskal-Wallis test for numerical variables. A two-sided p-value of < 0.05 was considered significant. Receiver operator characteristic (ROC) - curves were drawn and optimal cut-off values are calculated. Confidence intervals are presented in brackets.

Ethical statement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology according to Shewan and Coats.[13]

RESULTS

Baseline characteristics

39 patients with TC were identified. 48 matched patients were included in the STEMI group and 34 matched patients in the NSTEMI group. Baseline characteristics are summarized in **Table 1**. Only one TC patient presented without ECG changes. Six TC patients (15%) had dynamic ECG changes, 14 (36%) presented with ST-segment elevation. Two patients had giant negative T-waves, 3 patients had ST-segment depression, 12 patients (32%) had T-inversion and one patient presented with new onset of left bundle branch block. Ejection fraction at baseline was significantly lower in the TC group (45%) compared to the STEMI (49%, p=0.02) and NSTEMI (55%, p<0.001) group. In the TC group 12 (32%) events were preceded by unusual emotional stress, 8 (21%) events happened after physical stress or surgery. In ten patients (27%), no trigger could be identified (detailed information is shown in **Table 2**). Patients with TC were treated in hospital for 4 days (IR: 3 – 6 days; **Table 2)**. In the TC group ejection fraction at baseline was 45% (IR: 40 – 50%) and increased significantly during follow-up to 65% (IR: 60 - 67; p<0.0001).

Biomarkers

TnT, CK, CK-MB and myoglobin were only slightly elevated in the TC study population compared to the other two groups (**Table 3 and Figure 1**). Peak C-reactive protein (CRP) values did not significantly different between the study groups and were 20 mg/l (6 – 58.3 mg/l) in the TC group, 29 mg/l (13 – 108 mg/l) in the STEMI group and 18 mg/l (6 – 37.5 mg/l) in the NSTEMI group.

Cardiac biomarker ratios

At admission a cut-off value of NT-proBNP (ng/l) / myoglobin (µg/l) ratio of 3.8, distinguished TC from STEMI with a sensitivity of 89% and specificity of 90%, while a

NT-proBNP (ng/l) / myoglobin (µg/l) ratio of 14 separated well between TC and NSTEMI with a sensitivity of 65% and a specificity of 90%, respectively (**Table 4**).

Best differentiation of TC and ACS was possible with the ratio of peak levels of NT-proBNP (ng/l) / TnT (µg/l). A cut-off value of NT-proBNP (ng/l) / TnT (µg/l) ratio of 2889, distinguished TC from STEMI with a sensitivity of 91% and specificity of 95%, while a NT-proBNP (ng/l) / TnT (µg/l) ratio of 5000 separated well between TC and NSTEMI with a sensitivity of 83% and a specificity of 95%, respectively (**Table 4**).

In-hospital mortality

Two patients died in the TC group: One died from hypoxic encephalopathy after prolonged resuscitation, one died from sepsis and renal failure. Within the STEMI group five patients died. Two died from hypoxic encephalopathy after prolonged resuscitation and three patients from cardiogenic shock. In the NSTEMI group two patients died. One died due to arrhythmia and cardiogenic shock the other patient died from hypoxic encephalopathy after resuscitation. There was no significant difference in overall mortality between the three study groups.

Follow-up

The patients in the TC group had a median follow-up of 33 months (IR: 12 – 44 months). Six patients were lost to follow-up. Three (8%) of the 39 TC patients experienced recurrent episodes (**Table 2**). In these 3 TC patients normalization of ejection fraction after their first Takotsubo event had been documented by echocardiography. The event-free period varied widely from 14 months up to six years. In one female patient generalized tonic-clonic seizure was the cause of two Takotsubo events. In a second female patient, the trigger of the first Takotsubo event was prior pulmonary surgery, while the second event was heralded by respiratory

failure due to chronic obstructive lung disease. In one male patient no certain triggering event could be identified neither for the first nor second episode of TC.

DISCUSSION

This study demonstrates that in patients with Takotsubo cardiomyopathy a unique NT-proBNP / myoglobin or NT-proBNP / TnT ratio provides additional diagnostic information for an early and, potentially, non-invasive diagnosis of TC with a high sensitivity and specificity.

Our observations go along with findings of Madhavan *et al.*, who evaluated the neurohumoral and cardiac biomarker profile in patients with TC and compared it to patients with ST-elevation myocardial infarction.[7] They could demonstrate that patients with STEMI had lower BNP levels and greater elevations of troponin T and CK-MB, compared to the TC group. Takotsubo cardiomyopathy could be distinguished from STEMI by calculating the BNP / peak troponin T ratio with a sensitivity of 94% and a specificity of 100%.[7] However, their study had several limitations: First, BNP was measured only once on day one or two, and second TnT levels were assessed upon admission and once a day thereafter. Additionally, the sample size was small with only 19 TC patients and 10 patients with STEMI, while patients with NSTEMI were not included.[7]

It was therefore the object of our study to delineate a unique biomarker profile reflecting Takotsubo cardiomyopathy that would be commonly available and reliable enough to distinguish patients with stress-induced cardiomyopathy from those with STEMI or NSTEMI.

To investigate, whether the ratio of cardiac biomarkers is of diagnostic value, we retrospectively analyzed the ratio of NT-proBNP and several cardiac biomarkers in patients with TC, STEMI or NSTEMI: The NT-proBNP / myoglobin ratio at admission might be of use in the emergency department setting, as it emerged as the earliest marker to identify patients with TC. However, NT-proBNP / myoglobin ratio has a sensitivity of 89% at a specificity of 90% for discrimination of TC from STEMI and a sensitivity of 65% at a specificity of 90% to distinguish TC from NSTEMI. In this

context, it is important to be aware that myoglobin levels will peak approximately two to six hours after onset of pain.[14, 15]

Of note, to distinguish acute coronary syndromes from Takotsubo at the highest specificity and sensitivity, the use of the peak NT-proBNP / peak TnT ratio appeared most accurate. However, in our study population NT-proBNP levels usually peaked 22 – 26 hours after a cardiac event, whereas TnT levels peak 8 to 13 hours after the first manifestation of chest pain. This delay is, for sure, not acceptable in the acute setting, but in many cases the patients are admitted to the emergency department >24 hours after the onset of pain. Further, the NT-proBNP / TnT peak level ratio has an additional diagnostic value to predict the evolution of left-ventricular function even before hospital discharge of the patient, as TC usually goes along with a favorable prognosis. The NT-proBNP peak / CK-MB peak ratio revealed a comparable specificity and sensitivity. Contrarily, NT-proBNP / CK-MB ratios obtained at admission, at day 1 and 2 proved to be inferior to the other biomarker ratios and should be omitted.

The mechanism of NT-proBNP release is very similar in TC and ACS, as NT-proBNP secretion is mainly provoked by myocardial stretch, caused by pump failure.[16] In contrast, markers of myocardial damage – like troponin, CK, CK-MB and myoglobin – will especially be elevated in the setting of membrane leakage caused by myocardial necrosis, whereas TC is characterized by reversible myocardial damage without necrosis.[17-19] Therefore, the typical constellation of TC is characterized by a steep increase of NT-proBNP due to the compromised left ventricular function in the presence of only slightly elevated markers of myocardial necrosis.

Larson et al. observed in 1335 patients who were referred to the emergency department for suspected STEMI, that a proportion of 1.1% of patients finally had TC

as the underlying condition.[20] Hence, cardiac catheterization was unnecessary in these patients.

We clearly state, that in patients who present with acute onset of typical chest pain and ST-elevation on ECG, immediate coronary angiography is warranted. Moreover, coronary artery disease will have to be excluded in all patients with suspected ACS. However, in hemodynamically stable patients presenting > 12 hours after onset of pain, non-invasive imaging methods might be preferred, if cardiac biomarker ratios suggest the presence of TC. In these patients, 64-slice multidetector computed tomography could be a suitable diagnostic tool to confirm the diagnosis of TC.[21-23]

Limitations

This study is retrospective in nature and reports on a small study population. However, due to the low frequency of the disease, in 14 comparable studies, the mean number of patients with TC was 20 (range: 9 to 88) compared to 39 in this study.[24]

Troponin and NT-proBNP assays might vary among different manufactures, which may lead to differing cut-off values.

CONCLUSION

Patients with Takotsubo cardiomyopathy exhibit a typical cardiac biomarker profile, which might serve as an additional tool to distinguish these patients from those with STEMI or NSTEMI at an early stage. Nevertheless, obstructive coronary artery disease has to be ruled out in any case, but preferably, with non-invasive imaging modalities.

ACKNOWLEDGEMENTS

This study was sponsored by the Swiss National Foundation (Grant: SNF32003B_130624/1).

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Table 1: Baseline characteristics of the three study groups.

	Takotsubo (n=39)	STEMI (n=48)	NSTEMI (n=34)	p-value
Age (years)	71 (57 – 77)	64.5 (53.3 – 73)	69 (57.8 – 77)	0.14
Female (n, %)	35 (90)	42 (88)	30 (88)	0.95
Body-Mass-Index (kg/m^2)	25.1 (22.1 – 26.8)	24.6 (22.6 – 27.1)	26 (23.7 – 29.3)	0.2
Symptoms at admission (n, %)				0.12
Typical chest pain	30 (77)	44 (92)	31 (91)	
Resuscitation	2 (5)	4 (8)	2 (6)	
Syncope	5 (13)	0	1 (3)	
Dyspnoe	1 (3)	0	0	
Time to hospital admission (hours)	7.5 (5.3 – 12.8)	6 (4 – 10)	10 (6.8 – 13.3)	0.13
Glomerular filtration rate (MDRD formula ml/min)	60 (60 – 60)	60 (55 – 60)	60 (60 – 60)	0.08
Hypertension (n, %)	24 (62)	24 (50)	22 (65)	0.23
Diabetes (n, %)				0.48
Non-insulin dependent	3 (8)	4 (8)	5 (15)	
Insulin dependent	1 (3)	1 (2)	0	
Diet only	0	4 (8)	2 (6)	
Smoker (n, %)				0.57
Current	10 (26)	16 (33)	10 (29)	
Former	5 (13)	5 (10)	1 (3)	
Hyperlipidemia (n, %)	13 (33)	24 (50)	14 (41)	0.22
Family history of CAD (n, %)	6 (15)	17 (35)	9 (27)	0.1
Culprit lesion (n, %)				
LAD		25 (52)	11 (32)	
RCX		6 (12.5)	12 (35)	
RCA		16 (33)	10 (29)	
Main stem		1 (2)	1 (3)	
LVEDP (mmHg)	22.5 (15 – 29)	25.0 (17.0 – 29.0)	19 (14.3 – 24.8)	0.31
Ejection fraction - baseline (%)	45 (40 – 50)	49 (42 – 60)	55 (49 – 60)	<0.001

Continuous variables are presented as median with interquartile range in brackets.

Table 2. Characteristic parameters of the Takotsubo study population.

	Takotsubo (n=39)
Type of Takotsubo	
Apical ballooning	29 (74)
Midventricular	9 (23)
Lateral/apical	1 (3)
Ejection fraction - baseline (%)	45 (40 – 50)
Ejection fraction - follow-up (%)	65 (60 – 67)
Echo follow-up (months)	3 (1.0 – 11.3)
Clinical follow-up (months)	33 (12 – 44)
Hospitalization (days)	4 (3 – 6)
Trigger of Takotsubo event (n, %)	
Seizure	2 (5)
Death of relative	1 (3)
Psychosomatic	3 (8)
Stress in family	8 (21)
Syncope	3 (8)
Alcohol abstinence	2 (5)
Surgery	5 (13)
Physical stress	3 (8)
Unclear	10 (27)
Accident	2 (5)
Recurrent Takotsubo episode during clinical follow-up period (n, %)	3 (8)
3-years estimator of freedom from death or recurrent Takotsubo episodes (%)	84 ± 7.5

Continuous variables are presented as median with interquartile range in brackets.

Table 3: Time course of cardiac biomarkers in the three study groups.

	Takotsubo (n=39)	STEMI (n=48)	NSTEMI (n=34)	p-value
TnT at admission (µg/l)	0.34 (0.15 – 0.61)	2.55 (0.35 – 6.91)	1.02 (0.40 – 3.37)	<0.001
Myoglobin at admission	85.0 (46.0 – 167)	729 (359 – 2234)	506 (134 – 1032)	<0.001
TnT at day 1 (µg/l)	0.44 (0.20 – 0.68)	6.5 (2.58 – 9.46)	3.33 (1.24 – 6.35)	<0.001
TnT at day 2 (µg/l)	0.19 (0.09 – 0.37)	3.9 (2.63 – 6.27)	1.63 (1.03 – 3.25)	<0.001
CK-MB at day 1 (U/l)	36.0 (22.0 – 48.0)	258 (107 – 395)	137 (71.0 – 242)	<0.001
CK-MB at day 2 (U/l)	18.5 (15.0 – 26.3)	155 (83.5 – 253)	115 (58.0 – 197)	<0.001
CK at day 1 (U/l)	145 (92.5 – 239)	2006 (1251 – 3951)	1364 (615 –1751)	<0.001
CK at day 2 (U/l)	133 (75 – 161)	1402 (969 – 2169)	1094 (365 – 1689)	<0.001
NT-proBNP level at admission (ng/l)	1723 (754 – 5699)	461 (188 – 1451)	977 (499 – 2290)	0.001
NT-proBNP at day 1 (ng/l)	2164 (741 – 6999)	1231 (431 – 2579)	1375 (873 – 2465)	0.13
NT-proBNP at day 2 (ng/l)	6112 (2992 – 8153)	2549 (1691 – 5661)	1991 (996 – 4248)	0.006

Continuous variables are presented as median with interquartile range in brackets.

Table 4: Cut-off values with corresponding specificity and sensitivity.

Cut-off values for differentiation of Takotsubo and STEMI				
	Cut-off specificity 95%	**Specificity 95%**	**Area under the curve**	**95% confidence interval**
NT-proBNP (ng/l) / myoglobin (µg/l) at admission	12	sensitivity: 65%	0.951	0.899 – 1.000
peak NT-proBNP (ng/l) / peak TnT (µg/l)	2889	sensitivity: 91%	0.980	0.783 – 0.984
peak NT-proBNP (ng/l) / peak CK-MB (µg/l)	42	sensitivity: 86%	0.968	0.813 – 0.976
Cut-off values for differentiation of Takotsubo and NSTEMI				
	Cut-off specificity 95%	**Specificity 95%**	**Area under the curve**	**95% confidence interval**
NT-proBNP (ng/l) / myoglobin (µg/l) at admission	17	sensitivity: 58%	0.840	0.735 – 0.948
peak NT-proBNP (ng/l) / peak TnT (µg/l)	5000	sensitivity: 83%	0.977	0.698 – 0.953
peak NT-proBNP (ng/l) / peak CK-MB (µg/l)	78	sensitivity: 82%	0.955	0.579 – 0.942

Figure 1: Time course of different cardiac biomarkers over a three days time frame after an event. (see also corresponding Table 3.)